STEREOCONTROLLED SYNTHESIS OF 1β-AMINOALKYLCARBAPENEMS AND TRICYCLIC CARBAPENEMS (TRINEMS)

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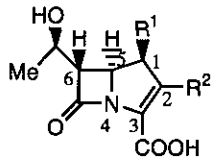
Abstract - The effective synthesis of 1β-aminoalkylcarbapenems and trinems are described and the antibacterial activities of new carbapenem derivatives prepared by this advantageous synthetic method are also reported.

Since the 1β-methyl carbapenems represented by Meropenem[1] and S-4661[2] were recognized as a new generation of β-lactam antibiotics because of their enhanced chemical and metabolic stabilities without the lack of potent antibacterial activity against a wide range of bacteria, much effort has been expended in seeking for better substituents at the 1-position in the carbapenem skeleton.[3] Recently, the Bristol-Myers Squibb group reported that a primary amino group in the side chain at the 1β-position contributed greatly to enhancing the antibacterial activity particularly against *Pseudomonas aeruginosa*.[4] This finding led us to devise an efficient and practical synthetic route for the synthesis of various kinds of 1β-functionalized alkylcarbapenems including highly stereoselective construction of an aminoalkyl group at the 1β-position. (Figure 1)

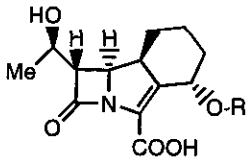
Previously, Uyeo *et al.* in our Shionogi group reported an excellent and practical stereocontrolled method for constructing the 1β-methyl group in the 1β-methylcarbapenem derivatives (e.g. 1).[5] We have applied this effective method to the synthesis of not only 1β-aminoalkyl carbapenems but also trinems which were first reported as a new type of tricyclic β-lactams by the Glaxo group,[6] and successfully obtained the expected compounds with efficiency. In particular, the synthesis of trinems are now being investigated to resolve various problems[7] (e.g., low stereoselectivity, low yield and so on) and our advantageous method is excellent for the construction of the trinem ring system. (Figure 1)

The 1β-aminoethylcarbapenem (1a) was synthesized as shown in Scheme 1. Protection of 3-buten-1-ol as a starting material by *p*-methoxybenzyl (PMB) bromide and subsequent ozonolysis gave aldehyde (2). Baylis-Hillman vinyl alkylation reaction of 2 with methyl acrylate in the presence of 3-quinuclidinol as a catalyst and subsequent bromination by

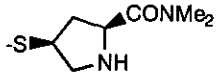
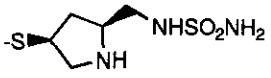
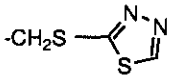
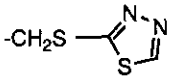
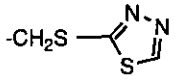
Figure 1.



1β-substituted carbapenems



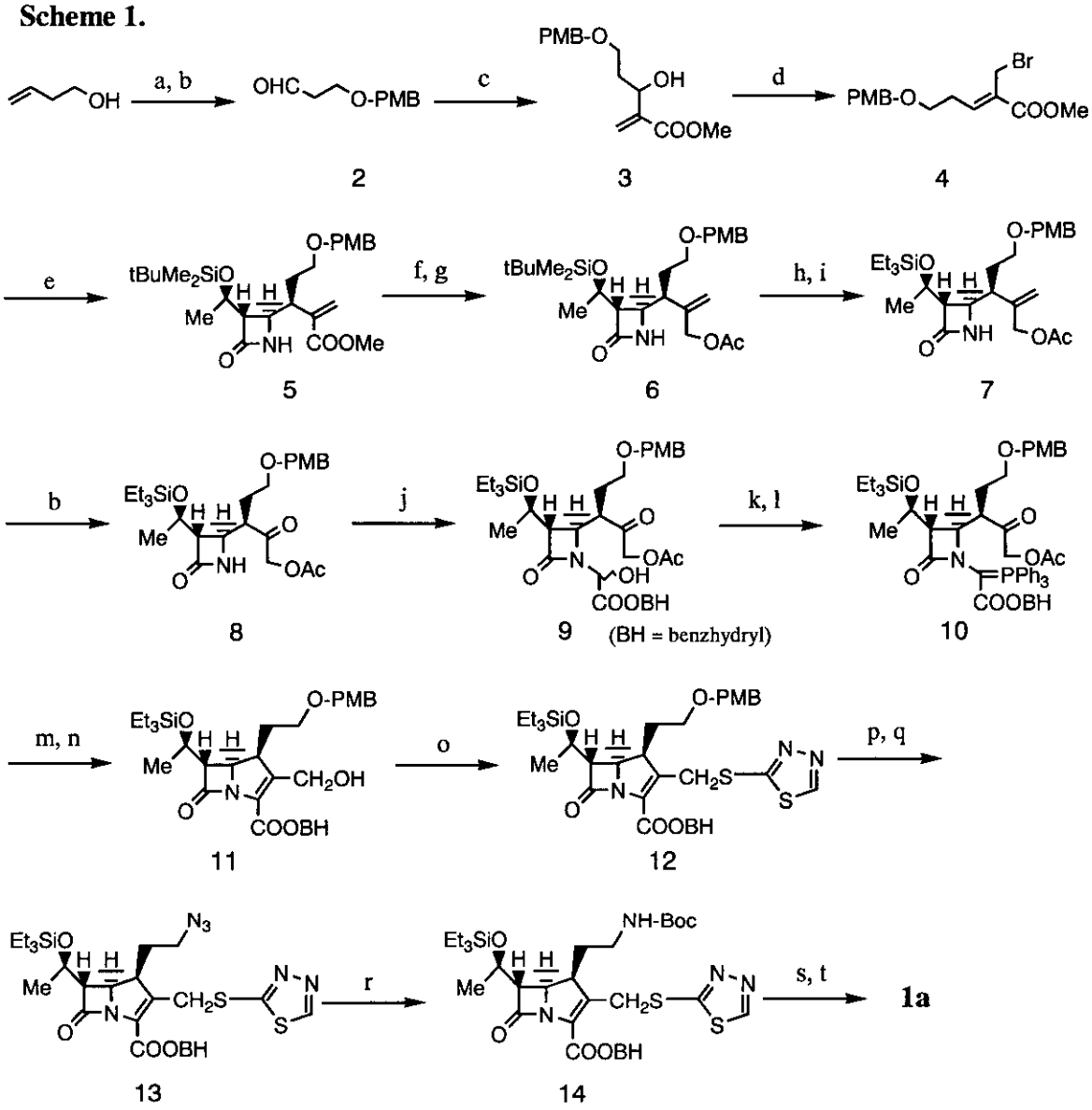
trinems

	R^1	R^2
Meropenem (MEPM)	-Me	
S-4661	-Me	
BMY-44041 (Bristol-Myers Squibb)	$-(CH_2)_3-NH_2$	$-S-(CH_2)_2-CN$
1	-Me	
1a	$-(CH_2)_2-NH_2$	
1b	$-(CH_2)_4-NH_2$	

	R
Sanfetrinem (GV-104326)	-Me
1c	-H (Sodium salt)

NBS and dimethyl sulfide gave the (Z)-configurated allylic bromide (4) which was the key compound to construct the 1β-side chain.[8] Next, 4 was coupled with a commercially available acetoxyazetidinone in the presence of zinc dust under Reformatsky reaction conditions to furnish a single isomer (5)[9] with complete stereoselectivity and high yield. After the methyl ester moiety of 5 had been converted to the acetoxy group by reduction with DIBAL-H and subsequent acetylation, the TBDMS group of 6 was replaced by triethylsilyl group to furnish 7. Successive preparation of the *N*-alkylated compound (9) was performed by ozonolysis of 7 and subsequent reaction with glyoxylic acid benzhydryl ester under azeotropic condition in toluene. Ylide formation of 9 with triphenylphosphine proceeded *via* the corresponding bromide to successfully furnish phosphorus ylide (10). Subsequently, deacetylation of 10 followed by intramolecular Wittig reaction gave the protected 1β-substituted carbapenem (11). After conversion of the hydroxymethyl group at the 2-position to the heteroaromatic thiomethyl group using the Mitsunobu reaction to furnish 12, the PMB ether was cleaved by DDQ and this deprotected derivative of 12 was successively converted to azide intermediate (13), which was then reduced to 14 with trimethylphosphine

Scheme 1.

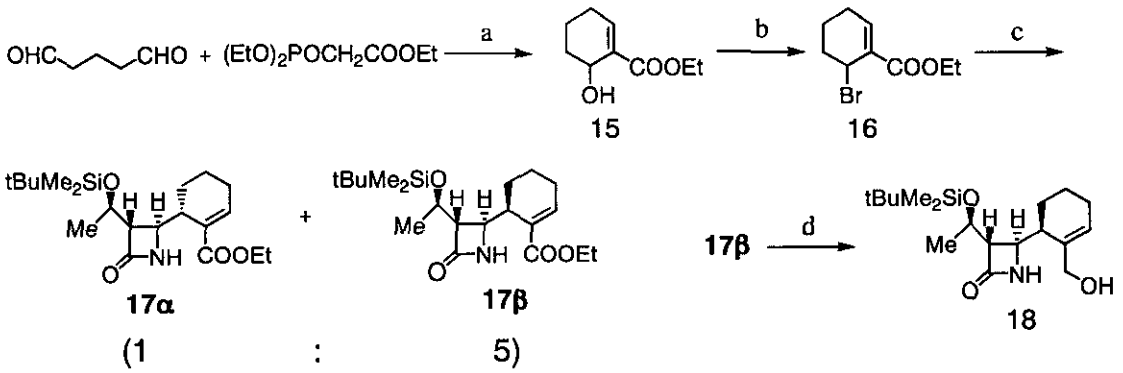


a) PMB-Br, NaH; b) i) O_3 in CH_2Cl_2/MeOH, -78℃, ii) Me_2S; c) methyl acrylate (2 eq.), 3-quinuclidinol (0.15 eq.), rt, 2 days; d) NBS (1.2 eq.), Me_2S (1.4 eq.), rt, 15 h; e) acetoxyazetidinone (1 eq.), Zn (1 eq.), DMF, rt, 2 h; f) DIBAL-H (3 eq.), toluene, -78℃; g) AcCl, Et_3N; h) conc. HCl(2 eq.)/AcOH(1 eq.), MeCN; i) Et_3SiCl, imidazole; j) glyoxylic acid benzhydryl ester (1 eq.), M.S.4A, reflux in toluene, 3 h; k) 2,6-lutidine (3 eq.), thionyl chloride (1.1 eq.), THF, -40℃, 30 min; l) 2,6-lutidine (2 eq.), NaBr (5 eq.), PPh_3 (1.2 eq.), rt, 1 h; m) NaOMe (0.2 eq.) MeOH, 0℃, 3 h; n) reflux in toluene, 3 h; o) PPh_3 (1.3 eq.), 2-mercapto-1,3,4-thiadiazole (1.3 eq.), DEAD (1.3 eq.), THF, 0℃, 40 min; p) DDQ (1.1 eq.), CH_2Cl_2/H_2O, 4 h; q) PPh_3 (1.3 eq.), HN_3 toluene solution (1.58 M, 1.3 eq.), DEAD (1.3 eq.), THF, 0℃, 1 h; r) PMe_3 THF solution (1 M, 2.6 eq), Boc_2O (10 eq.), THF/H_2O, rt, 15 h; s) Bu_4NF THF solution (1 M, 2 eq.), AcOH (3 eq.); t) $AlCl_3$ (10 eq.), anisole (10 eq.), CH_2Cl_2/CH_3NO_2, -60℃, 1 h

in THF/H_2O solvent system in the presence of di-*tert*-butyl dicarbonate (Boc_2O). The final deprotection step of **14** was performed by treatment with tetrabutylammonium fluoride and then with $AlCl_3$ in the presence of anisole[10] to give **1a**, which was purified by Diaion HP-20AG column chromatography.

The key intermediate (**18**), the same as that for 1β-(4-aminobutyl)carbapenem (**1b**) and trinem derivative (**1c**), was synthesized as shown in Scheme 2. The Horner-Wadsworth-Emmons olefination with glutaraldehyde and diethylphosphonoacetic acid ethyl ester[11] was performed to give the cyclic α,β-unsaturated carbonyl compound (**15**). After **15** was brominated by NBS and dimethyl sulfide, cyclic bromide (**16**) was coupled with acetoxy-azetidinone in the presence of zinc dust using THF as a solvent to predominantly give 1β-isomer (**17β**).[12] (The ratio of 1α-isomer (**17α**) and 1β-isomer (**17β**) was 1 : 5. These isomers could be separated by silica gel chromatography.) Next, 1β-isomer (**17β**) was reduced by DIBAL-H to furnish the key intermediate (**18**).

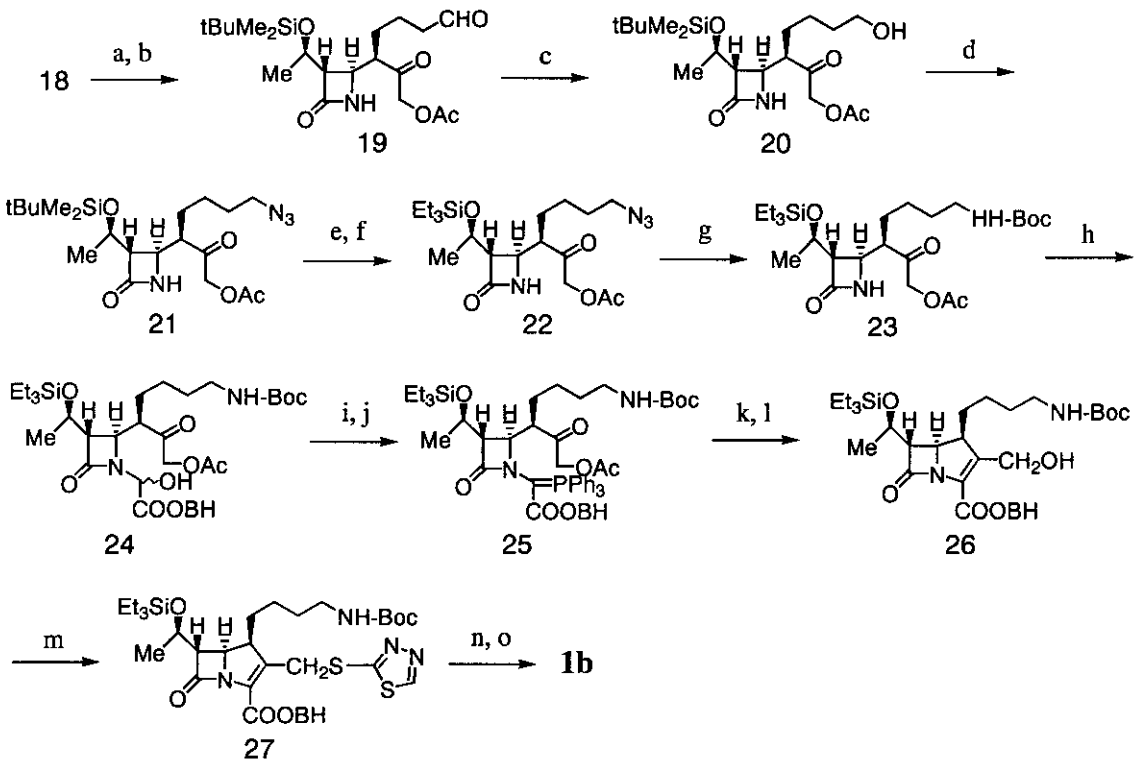
Scheme 2.



a) K_2CO_3aq. (1.6 eq.), rt, 15 h; b) NBS (1.1 eq.), Me_2S (1.2 eq.), rt, 3 h; c) acetoxyazetidinone (0.87 eq.), Zn (1.1 eq.), THF, rt, 1 h; d) DIBAL-H (3 eq.), toluene, -78℃

The following synthetic route to 1β-(4-aminobutyl)carbapenem (**1b**) is shown in Scheme 3. Acetylation and subsequent ozonolysis of **18** gave the ring-opened aldehyde (**19**) with high yield. Only the formyl group of **19** was reduced successfully with $NaBH_4$ in EtOH/CH_2Cl_2 solvent system[13] to furnish **20** (under these conditions, the ketone group in **19** was not affected.), and conversion of the hydroxy group to the azide group was performed by Mitsunobu reaction to give **21**. Subsequent replacement of the silyl group protecting the hydoxyethyl moiety as described above and hydogenation of azide (**22**) with Pd/C in the presence of Boc_2O furnished **23**. The final product (**1b**) was successfully synthesized from **23** *via* phosphorus ylide formation, intramolecular Wittig reaction, substitution at the 2-position by Mitsunobu reaction and final deprotection, using the methods employed for the synthesis of the 1β-aminoethyl derivative (**1a**).

Scheme 3.

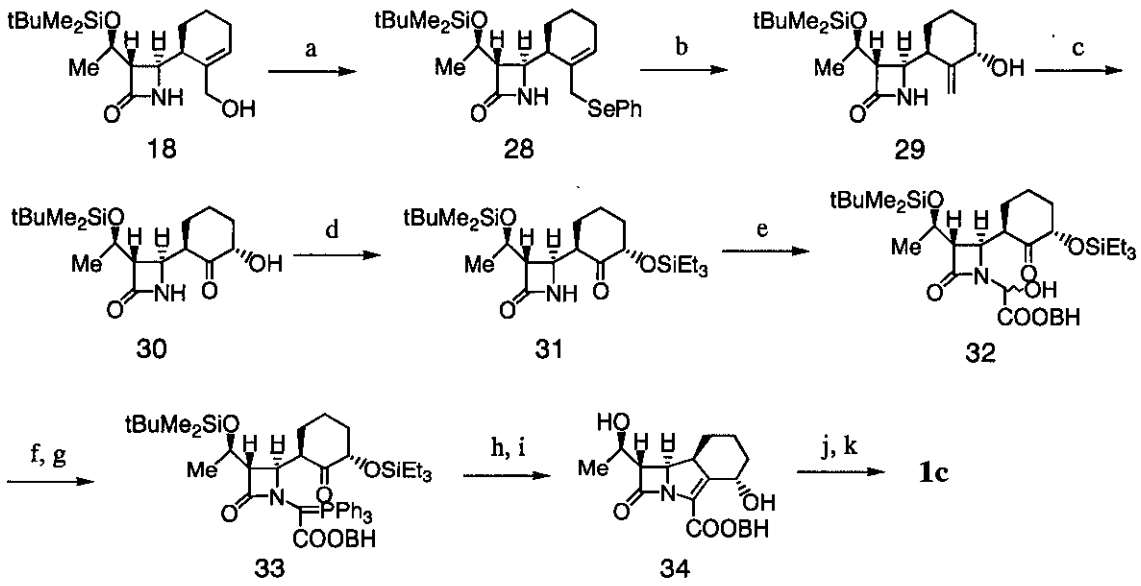


a) AcCl, Et_3N; b) i) O_3 in CH_2Cl_2/MeOH, -78℃, ii) Me_2S; c) $NaBH_4$ (1.5 eq.) / EtOH:CH_2Cl_2=3:7, -78℃, 40 min; d) PPh_3 (1.3 eq.), HN_3 toluene solution (1.58 M, 1.3 eq.), DEAD (1.3 eq.), THF, 0℃, 1 h; e) conc. HCl (2 eq.)/AcOH (1 eq.), MeCN; f) Et_3SiCl, imidazole; g) H_2, 5% Pd/C, Boc_2O (5 eq.), MeOH, 15 min; h) glyoxylic acid benzhydryl ester (1 eq.), M.S.4A, reflux in toluene, 3 h; i) 2,6-lutidine (3 eq.), thionyl chloride (1.1 eq.), THF, -40℃, 30 min; j) 2,6-lutidine (2 eq.), NaBr (5 eq.), PPh_3 (1.2 eq.), rt, 4 h; k) NaOMe (0.2 eq.), MeOH, 0℃, 5 h; l) reflux in toluene, 3 h; m) PPh_3 (1.3 eq.), 2-mercapto-1,3,4-thiadiazole (1.3 eq.), DEAD (1.3 eq.), THF, 0℃, 30 min; n) Bu_4NF THF solution (1 M, 2 eq.), AcOH (3 eq.); o) $AlCl_3$ (10 eq.), anisole (10 eq.), CH_2Cl_2/$MeNO_2$, -60℃, 1 h

The synthetic route of trinem derivative (1c) from the key intermediate (18) is shown in Scheme 4. After the hydroxy group of 18 was converted to the phenylselenyl group by treatment with tri-*n*-butylphosphine and *N*-(phenylseleno)phthalimide, selenide (28) thus obtained was oxidized by H_2O_2 in pyridine to give alcohol (29) almost as a single α-isomer,[14] *via* the Evans rearrangement.[15] After ozonolysis of 29 and subsequent protection of the hydroxy group by triethylchlorosilane, a series of ylide formation steps furnished phosphorus ylide (33). Desilylation of 33 and the subsequent intramolecular Wittig reaction successfully gave the protected trinem (34), then the final deprotection as described above and addition of equivalent $NaHCO_3$ furnished the trinem derivative 1c as sodium salt.

Our new method is effective for synthesizing 1β-functionalized alkylcarbapenems and trinems. It shows excellent stereoselectivity in constructing the 1β-substituent and offers a wide range of applications toward the synthesis for various 1β-substituted

Scheme 4.



a) *n*-Bu_3P (1.4 eq.), *N*-(phenylseleno)phthalimide (1.3 eq.), CH_2Cl_2, -78℃, 1 h; b) 30% H_2O_2aq, pyridine, rt, 30 min; c) i) O_3 in CH_2Cl_2/MeOH, -78℃, ii) Me_2S; d) Et_3SiCl, imidazole; e) glyoxylic acid benzhydryl ester (1 eq.), M.S.4A, reflux in toluene, 3 h; f) 2,6-lutidine (3 eq.), thionyl chloride (1.1 eq.), THF, -40℃, 30 min; g) 2,6-lutidine (2 eq.), NaBr (5 eq.), PPh_3 (1.2 eq.), rt, 4 h; h) conc. HCl (2 eq.)/AcOH (1 eq.) MeCN; i) reflux in toluene, 3 h; j) $AlCl_3$ (10 eq.), anisole (10 eq.), $CH_2Cl_2/MeNO_2$, -60℃, 1 h, k) $NaHCO_3$

carbapenems including trinems.

Table 1. Antibacterial activity (MIC, μg/mL) of carbapenem compounds

Organism	MIC (μg/mL)				
	1a	**1b**	**1**	**MEPM**	**S-4661**
S.a.	0.2	0.05	0.0125	0.1	0.02
S.a.(L)	1.6	0.4	0.1	0.8	0.2
S.a.(H)	25	6.3	3.1	50	25
E.f.	1.6	3.1	0.8	6.3	6.3
E.c.	0.05	0.05	0.2	0.02	0.02
P.v.	0.4	0.1	0.05	0.05	0.1
E.cl.	0.4	0.4	0.4	0.05	0.05
S.m.	0.2	0.4	0.8	0.05	0.1
P.a.	1.6	3.1	12.5	0.1	0.1

S.a., *Staphylococcus aureus* FDA 209P JC-1; *S.a.*(L), *Staphylococcus aureus* SR3131; *S.a.*(H), *Staphylococcus aureus* SR3626; *E.f.*, *Enterococcus faecalis* SR1004; *E.c.*, *Escherichia coli* NIHJ JC-2; *P.v.*, *Proteus vulgaris* CN-329; *E.cl.*, *Enterobacter cloacae* A 13880; *S.m.*, *Serratia marcescens* ATCC 13880; *P.a.*, *Pseudomonas aeruginosa* SR24.

The *in vitro* antibacterial activities of 1β-aminoalkyl analogues prepared as above are listed in Table 1 with values of MIC (μg/mL) against Gram-positive and Gram-negative bacteria including *Pseudomonas aeruginosa*. For comparison, the MIC values of 1[3] which is the 1β-methyl analogue of **1a** and **1b**, Meropenem (MEPM) and S-4661 are also listed. As expected, introduction of the aminoalkyl group at the 1β-position of the carbapenem skeleton contributes to enhancement of *anti-pseudomonal* activity, but also tends to cause a slight decrease in the activity against most other bacteria; compare **1a** and **1b** with **1**.

EXPERIMENTAL

Chemistry

IR spectra were taken on a Jasco IR-700 spectrophotometer. ^{1}H NMR spectra were recorded at 200 MHz on a Varian VXR-200 NMR spectrometer using TMS or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (in D_2O) as an internal standard. All reactions under anhydrous conditions were carried out using anhydrous solvents dried over Molecular Sieves type 4A in a nitrogen atmosphere.

Measurement of *in vitro* antibacterial activity

MICs were determined by agar dilution method using test agar. An overnight culture of bacteria in tryptosoy broth was diluted to about 10^6 cells/mL with the same broth and inoculated with an inoculating device onto agar containing serial twofold dilutions of the test compounds. The organisms were incubated at 37 °C for 18~20 h. The MIC of a compound was defined as the lowest concentration that visibly inhibited growth.

3-*p*-Methoxybenzyloxypropionaldehyde (2)

After *p*-methoxybenzyl alcohol (PMB-OH) (100 mL) and 47% aqueous HBr (200 mL) were stirred vigorously at rt for 30 min, parted organic layer was taken and dried over $CaCl_2$ to give PMB-Br. To a mixture of 3-buten-1-ol (50 g, 0.693 mol) and the above PMB-Br (145 g, 0.75 mol) in 500 mL of DMF under ice cooling, NaH (60% oil suspension, 0.748 mol, suspended in 200 ml of DMF) was added dropwise. After being stirred at rt for 1 h, the reaction mixture was partitioned between EtOAc and 1 N HCl. The organic layer was taken, washed with saturated aqueous $NaHCO_3$ and saturated brine, dried over $MgSO_4$, and evaporated *in vacuo*. (usual work up). O_3 was entered into a solution of this residue (150 g) in CH_2Cl_2 (1 L) / MeOH (200 mL) cooled at -78° C for 1.5 h, then dimethyl sulfide (153 mL, 2.08 mol) was added dropwise. The mixture was allowed to warm up to rt and partitioned between EtOAc and water. The organic layer was taken, washed with water twice, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by silica gel chromatography (toluene-EtOAc = 25:1) to give **2** as a colorless oil (87 g, 65%). IR ($CHCl_3$) cm^{-1} 1670; ^{1}H NMR

($CDCl_3$) δ 2.68 (td, J= 6.2 Hz, J= 2.0 Hz, 2H), 3.79 (t, J= 6.0 Hz, 2H), 3.81 (s, 3H), 4.46 (s, 2H), 6.88 (d, J= 9.0 Hz, 2H), 7.25 (d, J= 8.6 Hz, 2H), 9.79 (t, J= 2.0 Hz, 1H).

2-(1-Hydroxy-3-*p*-methoxybenzyloxypropyl)acrylic acid methyl ester (3)

The reaction mixture of **2** (87 g, 0.448 mol) , methyl acrylate (101 mL, 1.12 mol) and 3-quinuclidinol (11.4 g, 0.09 mol) was stirred without the solvent at rt for 2 d. Toluene (1 L) was added to the reaction mixture and concentrated under reduced pressure to 150 mL. This toluene solution was charged to a silica gel chromatography column and purified (toluene-EtOAc = 16:1) to give **3** as a colorless oil (75.4 g, 60%). IR ($CHCl_3$) cm^{-1} 3410, 1700; ^1H NMR ($CDCl_3$) δ 1.78~1.93 (m, 1H), 1.98~2.12 (m, 1H), 3.66 (quint, J= 2.4 Hz, 2H), 3.76 (s, 3H), 3.81 (s, 3H), 4.45 (s, 2H), 4.61~4.71 (m, 1H), 5.93 (s, 1H), 6.28 (s, 1H), 6.88 (d, J= 9.0 Hz, 2H), 7.25 (d, J= 8.6 Hz, 2H).

(Z)-(2-Bromomethyl-5-*p*-methoxybenzyloxy) pent-2-enoic acid methyl ester (4)

To a suspension of NBS (57.5 g, 0.323 mol) in CH_2Cl_2 (750 mL), dimethyl sulfide (27.5 mL, 0.377 mol) was added at -30 °C. The reaction mixture was allowed to warm up to rt, stirred for 20 min at the same temperature, and cooled to -30 °C again. Toluene solution of **3** (75.4 g, 0.269 mol / 750 mL of toluene) was added dropwise to the above reaction mixture at -30 °C , then the reaction mixture was stirred for 15 h at rt, and partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic layer was taken, washed with saturated brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by silica gel chromatography (toluene-EtOAc = 50:1) to give **4** as a colorless oil (70.6 g, 76%). IR ($CHCl_3$) cm^{-1} 1702; ^1H NMR ($CDCl_3$) δ 2.59 (q, J= 7.0 Hz, 2H), 3.60 (t, J= 6.6 Hz, 2H), 3.80 (s, 3H), 3.81 (s, 3H), 4.23 (s, 2H), 4.46 (s, 2H), 6.88 (d, J= 8.6 Hz, 2H), 7.02 (t, J= 7.0 Hz, 1H), 7.25 (d, J= 8.4 Hz, 2H). FAB-MS (m/z) 365 $[M+Na]^+$.

(3*S*, 4*R*)-3-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-4-[(1*S*)-1-(2-*p*-methoxybenzyloxyethyl)-2-methoxycarbonylallyl]-2-azetidinone (5)

To a solution of **4** (70.6 g, 0.206 mol) in DMF (800 mL), acetoxyazetidinone (59.2 g, 0.206 mol) and zinc dust (13.5 g, 0.206 mol) were added, and the reacton mixture was stirred vigorously at rt for 2 h. After the usual work up of the reaction mixture, the residue was purified by silica gel chromatography (toluene-EtOAc = 8:1) to give **5** as a colorless foam (93 g, 92%). IR ($CHCl_3$) cm^{-1} 3380, 1754, 1680; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6H), 0.86 (s, 9H), 1.08 (d, J= 6.2 Hz, 3H), 1.85 (q, J= 6.4 Hz, 2H), 2.78 (br s, 1H), 2.95 (q, J= 7.2 Hz, 1H), 3.33~3.48 (m, 2H), 3.73 (s, 3H), 3.75~3.79 (m, 1H), 3.81 (s, 3H), 4.10~4.19 (m, 1H), 4.36 (s, 2H), 5.61 (s, 1H), 6.01 (br s, 1H (-NH-)), 6.32 (s, 1H), 6.87 (d, J= 8.6 Hz, 2H), 7.23 (d, J= 8.4 Hz, 2H). FAB-MS (m/z) 492 $[M+H]^+$.

(3*S*, 4*R*)-3-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-4-[(1*S*)-1-(2-*p*-methoxybenzyloxyethyl)-

2-acetoxymethylallyl]-2-azetidinone (6)

To a solution of 5 (90 g, 0.183 mol) in toluene (2 L) cooled to -78 °C, DIBAL-H (1.5 M toluene solution, 366 mL, 0.549 mol) and MeOH (67 mL, 1.65 mol) were added, then the reaction mixture was allowed to warm up to 0 °C. Subsequently water (60 mL, 3.3 mol) was added and the reaction mixture was stirred at rt for 1 h. After the precipitate was removed by filtration, the organic layer was dried over $MgSO_4$, and evaporated *in vacuo*. To a solution of the residue in CH_2Cl_2 (1 L) under ice cooling, triethylamine (38.3 mL, 0.275 mol) and acetyl chloride (18.2 mL, 0.256 mol) were added, and the reaction mixture was stirred at the same temperature for 15 min. After the usual work up of the reaction mixture, the residue was purified by silica gel chromatography (toluene-EtOAc = 6:1) to give 6 as a colorless foam (70 g, 76%). IR ($CHCl_3$) cm^{-1} 3420, 1730, 1680; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6H), 0.86 (s, 9H), 1.12 (d, J= 6.2 Hz, 3H), 1.72~1.83 (m, 2H), 2.07 (s, 3H), 2.36~2.43 (m, 1H), 2.82 (t, J= 2.0 Hz, 1H), 3.38~3.55 (m, 2H), 3.73 (dd, J= 8.2 Hz, J= 2.0 Hz, 1H), 3.81 (s, 3H), 4.12~4.25 (m, 1H), 4.40 (s, 2H), 4.51 (s, 2H), 5.05 (s, 1H), 5.25 (s, 1H), 5.94 (br s, 1H (-NH-)), 6.87 (d, J= 8.6 Hz, 2H), 7.22 (d, J= 8.3 Hz, 2H). FAB-MS (m/z) 506 $[M+H]^+$.

(3*S*, 4*R*)-3-[(1*R*)-1-Triethylsilyloxyethyl]-4-[(1*S*)-1-(2-*p*-methoxybenzyloxyethyl)-2-acetoxymethylallyl]-2-azetidinone (7)

To a solution of 6 (22.6 g, 44.7 mmol) in MeCN (450 mL) under ice cooling, conc. HCl (7.45 mL, 90 mmol) and acetic acid (2.6 mL, 45 mmol) were added. After being stirred for 30 min at the same temperature, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ (100 mL) and the organic layer was washed with saturated brine twice to give desilylated compound. To a solution of this compound in DMF (260 mL) under ice cooling, imidazole (4.56 g, 67.1 mmol) and triethylchlorosilane (10.5 mL, 62.6 mmol) were added, and the reaction mixture was stirred for 20 min at the same temperature. After the usual work up of the reaction mixture, the residue was purified by silica gel column chromatography (toluene-EtOAc = 8:1) to give 7 as a colorless foam (18 g, 80%). IR ($CHCl_3$) cm^{-1} 3400, 1740, 1700; ^1H NMR ($CDCl_3$) δ 0.59 (q, J= 7.8 Hz, 6H), 0.94 (t, J= 7.8 Hz, 9H), 1.14 (d, J= 6.2 Hz, 3H), 1.71~1.81 (m, 2H), 2.07 (s, 3H), 2.33~2.43 (m, 1H), 2.80 (dd, J= 3.4 Hz, J= 2.0 Hz, 1H), 3.38~3.53 (m, 2H), 3.70 (dd, J= 8.0 Hz, J= 2.0 Hz, 1H), 3.81 (s, 3H), 4.11~4.21 (m, 1H), 4.39 (s, 2H), 4.51 (s, 2H), 5.04 (s, 1H), 5.24 (s, 1H), 5.96 (br s, 1H (-NH-)), 6.87 (d, J= 8.6 Hz, 2H), 7.23 (d, J= 9.0 Hz, 2H).

(3*S*, 4*R*)-3-[(1*R*)-1-Triethylsilyloxyethyl]-4-[(1*S*)-1-(2-*p*-methoxybenzyloxyethyl)-2-oxo-3-acetoxypropyl]-2-azetidinone (8)

O_3 was entered into a solution of 7 (18 g, 35.6 mmol) in CH_2Cl_2 (700 mL) / MeOH (100 mL) cooled at -78° C for 40 min, then dimethyl sulfide (7.84 mL, 107 mmol) was added dropwise. The reaction mixture was allowed to warm up to rt and partitioned between EtOAc and water. The organic layer was taken, washed with water twice, dried over $MgSO_4$, and

evaporated *in vacuo*. The residue was purified by silica gel chromatography (toluene-EtOAc = 6:1) to give 8 as a colorless foam (12.4 g, 69%). IR (KBr) cm^{-1} 3400, 1756, 1714, 1672; ^1H NMR ($CDCl_3$) δ 0.59 (q, J = 7.8 Hz, 6H), 0.94 (t, J = 7.8 Hz, 9H), 1.19 (d, J = 6.0 Hz, 3H), 1.72~1.83 (m, 1H), 1.96~2.09 (m, 1H), 2.14 (s, 3H), 2.91 (dd, J = 3.0 Hz, J = 2.4 Hz, 1H), 2.95~3.02 (m, 1H), 3.40~3.54 (m, 2H), 3.78 (dd, J = 7.2 Hz, J = 2.1 Hz, 1H), 3.81 (s, 3H), 4.14 (quint, J = 6.0 Hz, 1H), 4.39 (s, 2H), 4.67 (s, 2H), 5.88 (br s, 1H (-NH-)), 6.87 (d, J = 7.8 Hz, 2H), 7.24 (d, J = 9.3 Hz, 2H). FAB-MS (m/z) 508 $[M+H]^+$.

(3*S*, 4*R*)-3-[(1*R*)-1-Triethylsilyloxyethyl]-4-[(1*S*)-1-(2-*p*-methoxybenzyloxyethyl)-2-oxo-3-acetoxypropyl]-1-(2-diphenylmethoxycarbonyl-1-hydroxyethyl)-2-azetidinone (9)

8 (8.65 g, 17 mmol) and glyoxylic acid benzhydryl ester (4.4 g, 18.7 mmol) were dissolved in toluene (140 mL) and the reaction mixture was refluxed with a condenser containing Molecular Sieves type 4A for 3 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography (toluene-EtOAc = 4:1) to give 9 as a colorless foam (11 g, 87%). IR ($CHCl_3$) cm^{-1} 3480, 1749, 1710, 1688; ^1H NMR ($CDCl_3$) δ 0.46 (q, J = 7.1 Hz, 6H × 1/2 (isomer A)), 0.54 (q, J = 7.1 Hz, 6H × 1/2 (isomer B)), 0.86 (t, J = 7.1 Hz, 9H × 1/2 (isomer A)), 0.92 (t, J = 7.1 Hz, 9H × 1/2 (isomer B)), 1.15 (d, J = 6.3 Hz, 3H × 1/2 (isomer A)), 1.22 (d, J = 6.3 Hz, 3H × 1/2 (isomer B)), 1.71~1.87 (m, 1H), 1.92~2.03 (m, 1H), 2.09 (s, 3H × 1/2 (isomer A)), 2.10 (s, 3H × 1/2 (isomer B)), 3.03~3.56 (m, 4H), 3.81 (s, 3H), 3.87~4.00 (m, 1H), 4.33~4.37 (m, 1H), 4.55~4.99 (m, 4H), 5.31 (d, J = 7.1 Hz, 1H × 1/2 (isomer A)), 5.66 (d, J = 7.1 Hz, 1H × 1/2 (isomer B)), 6.86~7.34 (m, 15H). FAB-MS (m/z) 770 $[M+Na]^+$.

(3*S*, 4*R*)-3-[(1*R*)-1-Triethylsilyloxyethyl]-4-[(1*S*)-1-(2-*p*-methoxybenzyloxyethyl)-2-oxo-3-acetoxypropyl]-1-(2-diphenylmethoxycarbonyl-1-triphenylphsphoranylideneethyl)-2-azetidinone (10)

To a solution of 9 (11 g, 14.7 mmol) in THF (220 mL) cooled -40 °C, 2,6-lutidine (5.14 mL, 44.1 mmol) and thionyl chloride (1.2 mL, 16.2 mmol) were added, and the reaction mixture was stirred for 30 min at the same temperature. After the usual work up of the reaction mixture, the residue was dissolved in THF (300 mL) under ice cooling. 2,6-Lutidine (3.42 mL, 29.4 mmol), NaBr (7.56 g, 73.5 mmol) and triphenylphosphine (4.63 g, 17.6 mmol) were successively added to the above solution, and the reaction mixture was stirred vigorously at rt for 1 h. After the usual work up, the residue was purified by silica gel chromatography (toluene-EtOAc = 6:1) to give 10 as a white solid (7 g, 48%). IR ($CHCl_3$) cm^{-1} 1751, 1717, 1686, 1640; ^1H NMR ($CDCl_3$) δ 0.46 (q, J = 7.4 Hz, 6H), 0.87 (t, J = 7.4 Hz, 9H), 1.13 (d, J = 6.3 Hz, 3H), 1.98~2.06 (m, 2H), 2.10 (s, 3H), 2.54~2.68 (m, 1H), 2.94~3.08 (m, 1H), 3.24~3.42 (m, 2H), 3.75~3.85 (m, 1H), 3.81 (s, 3H), 4.02~4.10 (m, 1H), 4.20~4.86 (m, 4H), 6.68~7.74 (m, 30H). FAB-MS (m/z) 992 $[M+H]^+$.

Benzhydryl (1*S*,5*S*,6*S*)-1-(2-*p*-methoxybenzyloxyethyl)-2-hydroxymethyl-6-[(1*R*)-1-triethylsilyloxyethyl]carbapen-2-em-3-carboxylate (11)

To a solution of **10** (7 g, 7 mmol) in MeOH (70 mL) cooled -20 °C, NaOMe (4.58 M MeOH solution, 0.3 mL (1.4 mmol)) was added, and the reaction mixture was stirred for 3 h under ice cooling. After the usual work up of the reaction mixture, the residue was purified by silica gel chromatography (toluene-EtOAc = 4:1) to give the deacetylated ylide (3.9 g, 59%). After this ylide was refluxed in toluene for 3 h, concentration of the reaction mixture and purification by silica gel chromatography (toluene-EtOAc = 3:1) gave **11** as a white solid (2.3 g, 49% from **10**). IR ($CHCl_3$) cm^{-1} 3436, 1770, 1706; ^1H NMR ($CDCl_3$) δ 0.61 (q, J = 7.8 Hz, 6H), 0.95 (t, J = 7.8 Hz, 9H), 1.21 (d, J = 6.3 Hz, 3H), 1.72~1.82 (m, 1H), 1.88~1.99 (m, 1H), 3.23 (dd, J = 5.4 Hz, J = 3.0 Hz, 1H), 3.35 (dd, J = 8.1 Hz, J = 6.0 Hz, 1H), 3.42~3.58 (m, 2H), 3.80 (s, 3H), 4.21 (dd, J = 10.2 Hz, J = 3.0 Hz, 1H), 4.26 (t, J = 6.0 Hz, 1H), 4.33~4.49 (m, 2H), 4.42 (s, 2H), 6.86 (d, J = 9.0 Hz, 2H), 6.90 (s, 1H), 7.15~7.58 (m, 12H). FAB-MS (m/z) 672 $[M+H]^+$.

Benzhydryl (1*S*,5*S*,6*S*)-1-(2-*p*-methoxybenzyloxyethyl)-2-(1,3,4-thiadiazol-2-yl)thiomethyl-6-[(1*R*)-1-triethylsilyloxyethyl]carbapen-2-em-3-carboxylate (12)

To a solution of **11** (690 mg, 1.03 mmol) in THF (10 mL) under ice cooling, triphenylphosphine (351 mg, 1.34 mmol), 2-mercapto-1,3,4-thiadiazole (158 mg, 1.34 mmol) and diethyl azodicarboxylate (DEAD) (0.21 mL, 1.34 mmol) were successively added, and the reaction mixture was stirred for 40 min at the same temperature. After the reaction mixture was diluted with toluene (40 mL) and concentrated to 10 mL, the resulting crystals were removed by filtration. The filtrate was purified by silica gel chromatography (toluene-EtOAc = 4:1) to give **12** as a white solid (770 mg, 97%). IR ($CHCl_3$) cm^{-1} 1772, 1727, 1688; ^1H NMR ($CDCl_3$) δ 0.60 (q, J = 7.8 Hz, 6H), 0.94 (t, J = 7.8 Hz, 9H), 1.18 (d, J = 6.4 Hz, 3H), 1.63~1.79 (m, 1H), 1.96~2.05 (m, 1H), 3.23~3.31 (m, 2H), 3.40~3.52 (m, 2H), 3.80 (s, 3H), 4.09~4.22 (m, 2H), 4.17, 4.93 (ABq, J = 14.0 Hz, 2H), 4.39 (s, 2H), 6.85 (d, J = 9.6 Hz, 2H), 6.91 (s, 1H), 7.17~7.58 (m, 12H), 8.86 (s, 1H). FAB-MS (m/z) 772 $[M+H]^+$.

Benzhydryl (1*S*,5*S*,6*S*)-1-(2-azidoethyl)-2-(1,3,4-thiadiazol-2-yl)thiomethyl-6-[(1*R*)-1-triethylsilyloxyethyl]carbapen-2-em-3-carboxylate (13)

To a solution of **12** (250 mg, 0.32 mmol) in CH_2Cl_2 (5 mL) / water (0.25 mL) under ice cooling, DDQ (80 mg, 0.35 mmol) was added, and the reaction mixture was stirred vigorously at the same temperature for 4 h. After removal of the precipitate and the usual work up of the filtrate, the residue was purified by silica gel chromatography (toluene-EtOAc = 3:1) to give deprotected alcohol as colorless crystals (170 mg, 82%). To a solution of this alcohol (170 mg, 0.26 mmol) in THF (3 mL) under ice cooling, triphenylphosphine (89 mg, 0.34 mmol), HN_3 (1.58 M toluene solution, 0.21 mL, 0.34 mmol) and diethyl azodicarboxylate (DEAD) (0.053 mL, 0.34 mmol) were successively added, and the reaction mixture was stirred for 1 h at the

same temperature. After the reaction mixture was diluted with toluene (30 mL) and concentrated to 10 mL, the resulting crystals were removed by filtration. The filtrate was purified by silica gel chromatography (toluene-EtOAc = 16:1) to give **13** as colorless crystals (140 mg, 66% from **12**). IR ($CHCl_3$) cm^{-1} 2094, 1774, 1700; ^1H NMR ($CDCl_3$) δ 0.62 (q, J= 7.4 Hz, 6H), 0.96 (t, J= 7.4 Hz, 9H), 1.33 (d, J= 6.0 Hz, 3H), 1.57~1.77 (m, 1H), 2.02~2.15 (m, 1H), 3.22 (dd, J= 6.6 Hz, J= 2.6 Hz, 1H), 3.28~3.36 (m, 2H), 3.40~3.50 (m, 1H), 4.15~4.26 (m, 2H), 4.23, 4.96 (ABq, J= 14.0 Hz, 2H), 6.92 (s, 1H), 7.24~7.56 (m, 10H), 8.95 (s, 1H). *Anal.* Calcd for $C_{33}H_{40}N_6O_4S_2Si$: C,58.55; H,5.96; N,12.41. Found: C,58.46; H,5.97; N,12.33.

Benzhydryl (1*S*,5*S*,6*S*)-1-(2-*tert*-butoxycarbonylaminoethyl)-2-(1,3,4-thiadiazol-2-yl)thiomethyl-6-[(1*R*)-1-triethylsilyloxyethyl]carbapen-2-em-3-carboxylate (14)

To a solution of **13** (330 mg, 0.5 mmol) in THF (9 mL) under ice cooling, di-*tert*-butyl dicabonate (Boc_2O) (1.15 mL, 5 mmol), water (3.3 mL) and trimethylphosphine (1M THF solution, 1.3 mL, 1.3 mmol) were successively added, and the reaction mixture was stirred at rt for 15 h. After the usual work up of the reaction mixture, the residue was purified by silica gel chromatography (toluene-EtOAc = 4:1) to give **14** as a white solid (150 mg, 40%). IR ($CHCl_3$) cm^{-1} 3456, 1773, 1712, 1690; ^1H NMR ($CDCl_3$) δ 0.62 (q, J= 7.8 Hz, 6H), 0.92 (t, J= 7.8 Hz, 9H), 1.32 (d, J= 6.3 Hz, 3H), 1.41 (s, 9H), 1.52~1.61 (m, 1H), 1.91~2.03 (m, 1H), 2.97~3.07 (m, 1H), 3.10~3.27 (m, 2H), 3.52 (br s, 1H), 4.18~4.26 (m, 1H), 4.22, 4.96 (ABq, J= 16.5 Hz, 2H), 4.31~4.38 (m, 1H), 4.79 (br s, 1H (Boc-NH-)), 6.90 (s, 1H), 7.24~7.58 (m, 10H), 8.94 (s, 1H). SI-MS (m/z) 751 $[M+H]^+$.

(1*S*,5*S*,6*S*)-1-(2-Aminoethyl)-2-(1,3,4-thiadiazol-2-yl)thiomethyl-6-[(1*R*)-1-hydroxyethyl]-carbapen-2-em-3-carboxylic acid (1a)

To a solution of **14** (150 mg, 0.2 mmol) in THF (5 mL) under ice cooling, AcOH (0.035 mL, 0.6 mmol) and tetrabutylammonium fluoride (1M THF solution, 0.4 mL, 0.4 mmol) were added, and the reaction mixture was stirred at the same temperature for 2 h. After the usual work up of the reaction mixture, the residue was purified by silica gel chromatography (toluene-EtOAc = 1:1) to give desilylated compound as a white solid (60 mg, 50%). To a solution of this desilylated compound (60 mg, 0.094 mmol) in CH_2Cl_2 (6.3 mL) / $MeNO_2$ (2.1 mL) cooled to -20 °C, anisole (0.1 mL, 0.94 mmol) and $AlCl_3$ (1M $MeNO_2$ solution, 0.94 mL, 0.94 mmol) were added, and the reaction mixture was stirred vigorously for 1.5 h. After the reaction mixture was partitioned between NaOAc (239 mg, 2.9 mmol) in water (10 mL) and ether (10 mL), the aqueous layer was taken, washed with ether, and concentrated under reduced pressure to remove remaining organic solvent. Then, the residue was subjected to Diaion HP-20AG column chromatography and the fraction eluting with MeOH-water was lyophilized to give **1a** as a colorless foam (10 mg, 14% from **14**). IR (KBr) cm^{-1} 3420, 3300, 1756, 1630; ^1H NMR (D_2O) δ 1.31 (d, J= 6.2 Hz, 3H), 1.78~1.92 (m, 1H), 2.00~2.16 (m, 1H), 3.01~3.13 (m, 2H), 3.33~3.45 (m, 2H), 3.88, 4.73 (ABq, J= 14.8 Hz,

2H), 4.13~4.26 (m, 2H), 9.43 (s, 1H). SI-MS (m/z) 371 $[M+H]^+$. HR-FABMS Calcd for $C_{14}H_{19}N_4O_4S_2$ ($[M+H]^+$): 371.0848. Found: 371.0849. $[\alpha]_D$ -73.9 (c = 0.17, H_2O).

6-Hydroxycyclohex-1-enecarboxylic acid ethyl ester (15)

Aqueous K_2CO_3 (6.67 M, 183 mL, 1.22 mol) and diethylphosphonoacetic acid ethyl ester (121 mL, 0.607 mol) were added dropwise to glutaraldehyde (25% water solution, 305 g, 0.761 mol) keeping below 30 °C over a period of 3 h. The reaction mixture was stirred for 15 h at rt and extracted with ether (1.2 L). The organic layer was washed with water, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was distilled under reduce pressure to give **15** as a colorless oil (48.5 g, 47%, bp 100 °C / 3 mmHg). IR ($CHCl_3$) cm^{-1} 3576, 1698; ^1H NMR ($CDCl_3$) δ 1.31 (t, J = 7.2 Hz, 3H), 1.72~1.87 (m, 4H), 2.15~2.27 (m, 2H), 3.13 (d, J = 2.4 Hz, 1H (-OH)), 4.20 (q, J = 7.2 Hz, 2H), 4.54 (br s, 1H), 7.10 (t, J = 4.0 Hz, 1H).

6-Bromocyclohex-1-enecarboxylic acid ethyl ester (16)

To a suspension of NBS (55.8 g, 0.314 mol) in CH_2Cl_2 (700 mL) cooled to -30 °C, dimethyl sulfide (25.1 mL, 0.342 mol) was added at the same temperature. The reaction mixture was allowed to warm up to rt, stirred for 20 min at the same temperature, and cooled to -30 °C again. CH_2Cl_2 solution of **15** (48.5 g, 0.285 mol / 40 mL CH_2Cl_2) was added dropwise to the above mixture at -30 °C , then the reaction mixture was stirred for 2.5 h at rt, and partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic layer was taken, washed with saturated brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was distilled under reduce pressure to give **16** as a colorless oil (54.5 g, 82%, bp 110 °C / 3 mmHg). IR ($CHCl_3$) cm^{-1} 1710; ^1H NMR ($CDCl_3$) δ 1.33 (t, J = 7.2 Hz, 3H), 1.82~2.57 (m, 6H), 4.17~4.31 (m, 2H), 5.26 (br s, 1H), 7.07~7.10 (m, 1H). FAB-MS (m/z) 255 $[M+Na]^+$.

(3*S*, 4*R*)-3-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-4-[(1*R*)-2-ethoxycarbonylcyclohex-2-enyl]-2-azetidinone (17β)

To a solution of **16** (56.1 g, 0.2 mol) in THF (600 mL), acetoxyazetidinone (53.7 g, 0.23 mol) and zinc dust (16.5 g, 0.22 mol) were added, and the reacton mixture was stirred vigorously keeping below 40 °C for 1 h. After the usual work up of the reaction mixture, the residue was purified by silica gel chromatography (toluene-EtOAc = 8:1) to give **17β** as a colorless foam (22.5 g, 30%). IR ($CHCl_3$) cm^{-1} 3402, 1745, 1690; ^1H NMR ($CDCl_3$) δ 0.06 (s, 6H), 0.86 (s, 9H), 1.11 (d, J = 6.0 Hz, 3H), 1.29 (t, J = 7.2 Hz, 3H), 1.62~1.70 (m, 2H), 1.72~1.81 (m, 2H), 2.20~2.28 (m, 2H), 2.92 (dd, J = 4.5 Hz, J = 2.1 Hz, 1H), 3.20 (dd, J = 2.7 Hz, J = 1.2 Hz, 1H), 3.80 (dd, J = 6.9 Hz, J = 2.1 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 4.17~4.22 (m, 1H), 5.76 (br s, 1H (-NH-)), 7.11 (t, J = 3.9 Hz, 1H). FAB-MS (m/z) 382 $[M+H]^+$.

17α: IR ($CHCl_3$) cm^{-1} 3390, 1750, 1698; ^1H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.88 (s, 9H), 1.21 (d, J = 6.6 Hz, 3H), 1.31 (t, J = 7.5 Hz, 3H), 1.60~1.72 (m, 2H), 1.74~1.82 (m, 2H), 2.18~2.30 (m,

2H), 2.78 (m, 1H), 3.57 (d, J=6.9 Hz, 1H), 3.63 (dd, J= 6.9 Hz, J= 2.1 Hz, 1H), 4.14 (q, J= 7.5 Hz, 2H), 4.13~4.22 (m, 1H), 5.98 (br s, 1H (-NH-)), 7.19 (t, J= 1.2 Hz, 1H). FAB-MS (m/z) 382 $[M+H]^+$.

(3*S*, 4*R*)-3-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-4-[(1*R*)-2-hydroxymethylcyclohex-2-enyl]-2-azetidinone (18)

To a solution of **17β** (22.5 g, 59 mmol) in toluene (450 mL) cooled to -78 °C, DIBAL-H (1.5 M toluene solution, 118 mL, 177 mmol) and MeOH (21.5 mL, 0.53 mol) were added, then the reaction mixture was allowed to warm up to 0 °C. Subsequently water (19.1 mL, 1.06 mol) was added and the reaction mixture was stirred at rt for 1 h. After the precipitate was removed by filtration, the organic layer was dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by silica gel chromatography (toluene-EtOAc = 2:1) to give **18** as a colorless foam (12 g, 60%). IR ($CHCl_3$) cm^{-1} 3500, 3410, 1740; ^1H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.88 (s, 9H), 1.29 (d, J= 6.3 Hz, 3H), 1.58~1.73 (m, 4H), 1.87 (br s, 1H (-OH)), 2.07 (br s, 2H), 2.46 (br s, 1H), 3.14 (dd, J= 7.2 Hz, J= 1.2 Hz, 1H), 3.82 (dd, J= 6.3 Hz, J= 2.1 Hz, 1H), 4.04~4.23 (m, 3H), 5.85 (t, J= 3.6 Hz, 1H), 5.98 (br s, 1H (-NH-)). FAB-MS (m/z) 340 $[M+H]^+$.

(3*S*, 4*R*)-3-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-4-[(1*S*)-1-(3-formylpropyl)-2-oxo-3-acetoxypropyl]-2-azetidinone (19)

To a solution of **18** (6 g, 17.7 mmol) in CH_2Cl_2 (100 mL) under ice cooling, triethylamine (3 mL, 21.2 mmol) and acetyl chloride (1.44 mL, 20.4 mmol) were added, and the reaction mixture was stirred at the same temperature for 30 min. After the usual work up of the reaction mixture, the residue was purified by silica gel chromatography (toluene-EtOAc = 6:1) to give acetylated compound as a colorless foam (6.74 g, quant.). O_3 was entered into a solution of this compound in CH_2Cl_2 (210 mL) / MeOH (30 mL) cooled at -78° C for 30 min, then dimethyl sulfide (3.9 mL, 53.1 mmol) was added dropwise. The reaction mixture was allowed to warm up to rt and partitioned between EtOAc and water. The organic layer was taken, washed with water twice, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by silica gel chromatography (toluene-EtOAc = 1:2) to give **19** as a colorless foam (7 g, 95%). IR ($CHCl_3$) cm^{-1} 3400, 1754, 1729, 1690; ^1H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.88 (s, 9H), 1.17 (d, J= 6.3 Hz, 3H), 1.53~1.80 (m, 4H), 2.18 (s, 3H), 2.50 (t, J= 6.6 Hz, 2H), 2.80~2.88 (m, 1H), 2.92 (dd, J= 4.5 Hz, J= 2.1 Hz, 1H), 3.84 (dd, J= 6.9 Hz, J= 5.1 Hz, 1H), 4.12~4.20 (m, 1H), 4.70 (d, J= 4.8 Hz, 2H), 5.98 (br s, 1H (-NH-)), 9.76 (s, 1H). FAB-MS (m/z) 414 $[M+H]^+$.

(3*S*, 4*R*)-3-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-4-[(1*S*)-1-(4-hydroxybutyl)-2-oxo-3-acetoxypropyl]-2-azetidinone (20)

To a solution of **19** (6 g, 14.5 mmol) in CH_2Cl_2 (385 mL) / EtOH (165 mL) cooled to -78 °C, $NaBH_4$ (823 mg, 21.8 mmol) was added, then the reaction mixture was stirred for 40 min at

the same temperature. Subsequently water was added and the mixture was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. After the organic layer was dried over $MgSO_4$ and evaporated *in vacuo*, the residue was purified by silica gel chromatography (toluene-EtOAc = 1:2) to give **20** as a colorless foam (4.3 g, 71%). IR ($CHCl_3$) cm^{-1} 3398, 3360, 1749, 1683; ^1H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.88 (s, 9H), 1.17 (d, J= 6.3 Hz, 3H), 1.55~1.77 (m, 6H), 2.07 (t, J= 7.5 Hz, 1H (-OH)), 2.17 (s, 3H), 2.80 (dd, J= 6.0 Hz, J= 3.0 Hz, 1H), 2.93 (dd, J= 4.8 Hz, J= 2.4 Hz, 1H), 3.64 (t, J= 6.0 Hz, 2H), 3.82 (dd, J= 6.0 Hz, J= 4.5 Hz, 1H), 4.10~4.19 (m, 1H), 4.69 (d, J = 6.9 Hz, 2H), 6.09 (br s, 1H (-NH-)). FAB-MS (m/z) 416 $[M+H]^+$.

(3*S*, 4*R*)-3-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-4-[(1*S*)-1-(4-azidobutyl)-2-oxo-3-acetoxypropyl]-2-azetidinone (21)

To a solution of **20** (2.08 g, 5 mmol) in THF (42 mL) under ice cooling, triphenylphosphine (1.7 g, 6.5 mmol), HN_3 (1.58 M toluene solution, 4.1 mL, 6.5 mmol) and diethyl azodicarboxylate (DEAD) (1.02 mL, 6.5 mmol) were successively added, and the reaction mixture was stirred for 1 h at the same temperature. After the reaction mixture was diluted with toluene (200 mL) and concentrated to 20 mL, the resulting crystals were removed by filtration. The filtrate was purified by silica gel chromatography (toluene-EtOAc = 1:1) to give **21** as a colorless foam (1.8 g, 82%). IR ($CHCl_3$) cm^{-1} 3400, 2094, 1754, 1710; ^1H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.88 (s, 9H), 1.17 (d, J= 6.3 Hz, 3H), 1.40~1.87 (m, 6H), 2.12 (s, 3H), 2.80 (dd, J= 6.0 Hz, J= 3.0 Hz, 1H), 2.94 (dd, J= 4.5 Hz, J= 2.1 Hz, 1H), 3.24~3.33 (m, 2H), 3.82 (dd, J= 6.0 Hz, J= 1.8 Hz, 1H), 4.06~4.23 (m, 1H), 4.68 (s, 2H), 5.90 (br s, 1H (-NH-)). FAB-MS (m/z) 441 $[M+H]^+$.

(3*S*, 4*R*)-3-[(1*R*)-1-Triethylsilyloxyethyl]-4-[(1*S*)-1-(4-azidobutyl)-2-oxo-3-acetoxypropyl]-2-azetidinone (22)

To a solution of **21** (1.8 g, 4.09 mmol) in MeCN (44 mL) under ice cooling, conc. HCl (0.68 mL, 8.2 mmol) and acetic acid (0.24 mL, 4.09 mmol) were added. After being stirred for 2 h at the same temperature, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$. (20 mL) and the organic layer was washed with saturated brine twice. The residue was purified by silica gel column chromatography (toluene-EtOAc = 1:2) to give desilylated compound (1.1g, 82%). To a solution of this compound in DMF (20 mL) under ice cooling, imidazole (275 mg, 4.04 mmol) and triethylchlorosilane (0.62 mL, 3.71 mmol) were added, and the mixture was stirred for 30 min at the same temperature. After the usual work up of the reaction mixture, the residue was purified by silica gel column chromatography (toluene-EtOAc = 8:1) to give **22** as a colorless foam (1.3 g, 72% from **21**). IR ($CHCl_3$) cm^{-1} 3398, 2094, 1755, 1709; ^1H NMR ($CDCl_3$) δ 0.60 (q, J= 7.8 Hz, 6H), 0.95 (t, J= 7.8 Hz, 9H), 1.21 (d, J= 6.3 Hz, 3H), 1.30~1.85 (m, 6H), 2.18 (s, 3H), 2.78~2.84 (m, 1H), 2.93 (dd, J= 6.0

Hz, J = 2.7 Hz, 1H), 3.23~3.33 (m, 2H), 3.77 (dd, J = 6.0 Hz, J = 2.4 Hz, 1H), 4.08~4.16 (m, 1H), 4.69 (d, J = 3.0 Hz, 2H), 5.87 (br s, 1H (-NH-)). FAB-MS (m/z) 441 $[M+H]^+$.

(3*S*, 4*R*)-3-[(1*R*)-1-Triethylsilyloxyethyl]-4-[(1*S*)-1-(4-*tert*-butoxycarbonylaminobutyl)-2-oxo-3-acetoxypropyl]-2-azetidinone (23)

After the suspension of **22** (1.2 g, 2.72 mmol), di-*tert*-butyl dicabonate (Boc_2O) (3.12 mL, 13.6 mmol) and palladium on activated carbon (Pd/C) (Pd 5%, 240 mg) in MeOH (20 mL) was stirred vigorously under H_2 atmosphere for 15 min, Pd/C was removed and the filtrate was evaporated *in vacuo*. The residue was purified by silica gel chromatography (toluene-EtOAc = 1:1) to give **23** as a colorless foam (1.2 g, 86%). IR ($CHCl_3$) cm^{-1} 3400, 1753, 1720, 1700; ^1H NMR ($CDCl_3$) δ 0.60 (q, J = 8.0 Hz, 6H), 0.95 (t, J = 8.0 Hz, 9H), 1.20 (d, J = 6.2 Hz, 3H), 1.25~1.81 (m, 6H), 1.44 (s, 9H), 2.17 (s, 3H), 2.73~2.82 (m, 1H), 2.88 (dd, J = 6.0 Hz, J = 3.0 Hz, 1H), 3.03~3.16 (m, 2H), 3.77 (dd, J = 6.8 Hz, J = 2.0 Hz, 1H), 4.08~4.20 (m, 1H), 4.68 (d, J = 4.2 Hz, 2H), 6.10 (br s, 1H (-NH-)). FAB-MS (m/z) 515 $[M+H]^+$.

(3*S*, 4*R*)-3-[(1*R*)-1-Triethylsilyloxyethyl]-4-[(1*S*)-1-(4-*tert*-butoxycarbonylaminobutyl)-2-oxo-3-acetoxypropyl]-1-(2-diphenylmethoxycarbonyl-1-hydroxyethyl)-2-azetidinone (24)

23 (0.8 g, 1.55 mmol) and glyoxylic acid benzhydryl ester (375 mg, 2.48 mmol) were dissolved in toluene (15 mL) and this mixture was refluxed with a condenser containing Molecular Sieves type 4A for 3 h. The reaction mixture was concentrated under reduced pressure and purified by silica gel chromatography (toluene-EtOAc = 3:1) to give **24** as a colorless foam (0.9 g, 77%). IR ($CHCl_3$) cm^{-1} 3518, 3446, 1748, 1710, 1688; ^1H NMR ($CDCl_3$) δ 0.48 (q, J = 7.5 Hz, 6H × 1/2 (isomer A)), 0.55 (q, J = 7.5 Hz, 6H × 1/2 (isomer B)), 0.87 (t, J = 7.5 Hz, 9H × 1/2 (isomer A)), 0.93 (t, J = 7.5 Hz, 9H × 1/2 (isomer B)), 1.18 (d, J = 6.6 Hz, 3H × 1/2 (isomer A)), 1.26 (d, J = 6.6 Hz, 3H × 1/2 (isomer B)), 1.44 (s, 9H), 1.21~1.64 (m, 6H), 2.13 (s, 3H), 2.91~3.08 (m, 3H), 3.30~3.33 (m, 1H), 3.71~3.73 (m, 1H), 3.90~3.98 (m, 1H), 4.45~4.68 (m, 2H), 5.34 (d, J = 7.2 Hz, 1H × 1/2 (isomer A)), 5.67 (d, J = 7.2 Hz, 1H × 1/2 (isomer B)), 6.95 (s, 1H), 7.16~7.39 (m, 10H). FAB-MS (m/z) 777 $[M+Na]^+$.

(3*S*, 4*R*)-3-[(1*R*)-1-Triethylsilyloxyethyl]-4-[(1*S*)-1-(4-*tert*-butoxycarbonylaminobutyl)-2-oxo-3-acetoxypropyl]-1-(2-diphenylmethoxycarbonyl-1-triphenylphsphoranylideneethyl)-2-azetidinone (25)

To a solution of **24** (0.9 g, 1.19 mmol) in THF (20 mL) cooled to -40 °C, 2,6-lutidine (0.42 mL, 3.57 mmol) and thionyl chloride (0.1 mL, 1.31 mmol) were added, and the reaction mixture was stirred for 30 min at the same temperature. After the usual work up of the reaction mixture, the residue was dissolved in THF (30 mL) under ice cooling. 2,6-Lutidine (0.28 mL, 2.38 mmol), NaBr (612 mg, 5.95 mmol) and triphenylphosphine (375 mg, 1.43 mmol) were successively added to the solution, and the reaction mixture was stirred vigorously at rt for 4 h. After the usual work up, the residue was purified by silica gel chromatography (toluene-

EtOAc = 6:1) to give **25** as a white solid (550 mg, 46%). IR ($CHCl_3$) cm^{-1} 3442, 1738, 1705, 1682; ^1H NMR ($CDCl_3$) δ 0.40~0.56 (m, 6H), 0.83~0.93 (m, 9H), 1.20~1.30 (m, 3H), 1.44~1.48 (m, 9H), 1.22~1.68 (m, 6H), 2.10 (s, 3H), 2.47~2.62 (m, 1H), 2.85~3.03 (m, 3H), 3.73~3.85 (m, 1H), 4.03~4.15 (m, 1H), 4.50~4.60 (m, 2H), 6.96~7.76 (m, 26H). FAB-MS (m/z) 999 $[M+H]^+$.

Benzhydryl (1*S*,5*S*,6*S*)-1-(4-*tert*-butoxycarbonylaminobutyl)-2-hydroxymethyl-6-[(1*R*)-1-triethylsilyloxyethyl]carbapen-2-em-3-carboxylate (26)

To a solution of **25** (550 mg, 0.55 mmol) in MeOH (6 mL) cooled to -20 °C, NaOMe (4.58 M MeOH solution, 0.024 mL (0.11 mmol)) was added, and the reaction mixture was stirred for 5 h under ice cooling. After the usual work up of the reaction mixture, the residue was purified by silica gel chromatography (toluene-EtOAc = 2:1) to give the deacetylated ylide as a white solid (300 mg, 57%). After this ylide was refluxed in toluene (10 mL) for 3 h, concentration of the reaction mixture and purification by silica gel chromatography (toluene-EtOAc = 2:1) gave **26** as a white solid (160 mg, 43% from **25**). IR ($CHCl_3$) cm^{-1} 3444, 1769, 1704; ^1H NMR ($CDCl_3$) δ 0.62 (q, J = 7.5 Hz, 6H), 0.96 (t, J = 7.5 Hz, 9H), 1.32 (d, J = 6.0 Hz, 3H), 1.44 (s, 9H), 1.45~1.75 (m, 6H), 3.02~3.22 (m, 4H), 3.38 (br s, 1H (-OH)), 4.17~4.39 (m, 2H), 4.49~4.60 (m, 2H), 6.90 (s, 1H), 7.19~7.57 (m, 10H). FAB-MS (m/z) 679 $[M+H]^+$.

Benzhydryl (1*S*,5*S*,6*S*)-1-(4-*tert*-butoxycarbonylaminobutyl)-2-(1,3,4-thiadiazol-2-yl)thiomethyl-6-[(1*R*)-1-triethylsilyloxyethyl]carbapen-2-em-3-carboxylate (27)

To a solution of **26** (160 mg, 0.236 mmol) in THF (3 mL) under ice cooling, triphenylphosphine (80 mg, 0.31 mmol), 2-mercapto-1,3,4-thiadiazole (36 mg, 0.31 mmol) and diethyl azodicarboxylate (DEAD) (0.048 mL, 0.31 mmol) were successively added, and the reaction mixture was stirred for 30 min at the same temperature. After the reaction mixture was diluted with toluene (15 mL) and concentrated to 5 mL, the resulting crystals were removed by filtration. The filtrate was purified by silica gel chromatography (toluene-EtOAc = 2:1) to give **27** as a white solid (140 mg, 76%). IR ($CHCl_3$) cm^{-1} 3446, 1771, 1708; ^1H NMR ($CDCl_3$) δ 0.61 (q, J = 7.8 Hz, 6H), 0.95 (t, J = 7.8 Hz, 9H), 1.30 (d, J = 6.6 Hz, 3H), 1.44 (s, 9H), 1.35~1.85 (m, 6H), 3.07~3.13 (m, 4H), 4.13~4.31 (m, 2H), 4.22, 4.93 (ABq, J = 14.0 Hz, 2H), 6.91 (s, 1H), 7.19~7.58 (m, 10H), 8.94 (s, 1H). FAB-MS (m/z) 779 $[M+H]^+$.

(1*S*,5*S*,6*S*)-1-(4-Aminobutyl)-2-(1,3,4-thiadiazol-2-yl)thiomethyl-6-[(1*R*)-1-hydroxyethyl]-carbapen-2-em-3-carboxylic acid (1b)

Deprotection of **27** (140 mg, 0.18 mmol) was performed by the same method as preparation of **1a** to give **1b** as a colorless foam (15 mg, 21%). IR (KBr) cm^{-1} 3410, 3310, 1758, 1630; ^1H NMR (D_2O) δ 1.29 (d, J = 6.6 Hz, 3H), 1.45~1.73 (m, 6H), 2.99 (t, J = 7.5 Hz, 2H), 3.28 (td, J = 10.2 Hz, J = 3.0 Hz, 1H), 3.37 (dd, J = 6.6 Hz, J = 3.0 Hz, 1H), 3.88, 4.90 (ABq, J = 14.7 Hz,

2H), 4.11 (dd, J = 9.9 Hz, J = 3.0 Hz, 1H), 4.21 (quint, J = 6.6 Hz, 1H), 9.42 (s, 1H). SI-MS (m/z) 399 $[M+H]^+$. HR-FABMS Calcd for $C_{16}H_{23}N_4O_4S_2$ ($[M+H]^+$): 399.1161. Found: 399.1162. $[\alpha]_D$ -74.2 (c = 0.13, H_2O).

(3*S*, 4*R*)-3-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-4-[(1*R*)-2-phenylselenenylmethyl-cyclohex-2-enyl]-2-azetidinone (28)

To a solution of **18** (2.4 g, 7 mmol) in CH_2Cl_2 (60 mL) cooled to -78 °C, tri-*n*-butylphosphine (2.46 mL, 9.8 mmol) and *N*-(phenylseleno)phthalimide (2.78 g, 9.1 mmol) were added, and the reaction mixture was stirred at the same temperature for 1 h. After the precipitate was removed by filtration, the filtrate was evaporated *in vacuo* and the residue was purified by silica gel chromatography (toluene-EtOAc = 25:1) to give **28** as a pale yellow solid (2.9 g, 85%). IR ($CHCl_3$) cm^{-1} 3402, 1749; ^1H NMR ($CDCl_3$) δ 0.06 (s, 6H), 0.88 (s, 9H), 1.19 (d, J = 6.0 Hz, 3H), 1.37~1.60 (m, 4H), 1.79~1.90 (m, 2H), 2.60~2.65 (m, 1H), 2.95 (d, J = 6.6 Hz, 1H), 3.45~3.69 (m, 2H), 3.83 (dd, J = 5.7 Hz, J = 2.1 Hz, 1H), 4.04~4.12 (m, 1H), 5.47 (s, 1H), 5.72 (br s, 1H (-NH-)), 7.18~7.22 (m, 2H), 7.40~7.43 (m, 2H), 7.70~7.84 (m, 1H). FAB-MS (m/z) 480 $[M+H]^+$.

(3*S*, 4*R*)-3-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-4-[(1*R*,3*S*)-3-hydroxy-2-methylenecyclohexyl]-2-azetidinone (29)

To a solution of **28** (2.24 g, 4.68 mmol) in pyridine (31 mL), H_2O_2 (30% water solution, 10.6 mL, 93.6 mmol) was added, and the reaction mixture was stirred at rt for 30 min. After the usual work up of the reaction mixture, the residue was purified by silica gel chromatography (toluene-EtOAc = 2:1) to give **29** as colorless crystals (0.8 g, 50%). IR ($CHCl_3$) cm^{-1} 3500, 3404, 1753, 1646; ^1H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.88 (s, 9H), 1.12 (d, J = 6.3 Hz, 3H), 1.42~1.75 (m, 6H), 2.49~2.54 (m, 1H), 2.77~2.79 (m, 1H), 3.86 (dd, J = 8.4 Hz, J = 2.1 Hz, 1H), 4.12~4.17 (m, 2H), 4.78 (s, 1H), 5.00 (s, 1H), 5.78 (br s, 1H (-NH-)). *Anal.* Calcd for $C_{18}H_{33}NO_3Si$: C,63.67; H,9.80; N,4.13. Found: C,63.48; H,9.74; N,4.12.

(3*S*, 4*R*)-3-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-4-[(1*R*,3*S*)-3-hydroxy-2-oxocyclohexyl]-2-azetidinone (30)

O_3 was entered into a solution of **29** (1.2 g, 3.53 mmol) in CH_2Cl_2 (49 mL) / MeOH (7 mL) cooled at -78 °C for 10 min, then dimethyl sulfide (0.78 mL, 10.6 mmol) was added dropwise. The reaction mixture was allowed to warm up to rt and partitioned between EtOAc and water. The organic layer was taken, washed with water twice, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by silica gel chromatography (toluene-EtOAc = 1:1) to give **30** as colorless crystals (1 g, 83%). IR ($CHCl_3$) cm^{-1} 3490, 3402, 1761, 1710; ^1H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.88 (s, 9H), 1.03 (d, J = 6.3 Hz, 3H), 1.61~1.94 (m, 6H), 2.79~2.85 (m, 1H), 2.94 (t, J = 2.7 Hz, 1H), 3.45 (d, J = 3.3 Hz, 1H (-OH)), 4.04 (dd, J = 9.6 Hz,

J = 2.1 Hz, 1H), 4.18~4.25 (m, 2H), 5.94 (br s, 1H (-NH-)). *Anal.* Calcd for $C_{17}H_{31}NO_4Si$: C,59.79; H,9.15; N,4.10. Found: C,59.75; H,9.03; N,4.11.

(3*S*, 4*R*)-3-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-4-[(1*R*,3*S*)-3-triethylsilyloxy-2-oxocyclohexyl]-2-azetidinone (31)

To a solution of 30 (500 mg, 1.46 mmol) in DMF (10 mL) under ice cooling, imidazole (120 mg, 1.76 mmol) and triethylchlorosilane (0.27 mL, 1.61 mmol) were added, and the reaction mixture was stirred for 1 h at the same temperature. After the usual work up of the reaction mixture, the residue was purified by silica gel column chromatography (toluene-EtOAc = 4:1) to give 31 as a colorless foam (660 mg, quant.). IR ($CHCl_3$) cm^{-1} 3406, 1753, 1714; ^1H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.58 (q, J = 8.0 Hz, 6H), 0.87 (s, 9H), 0.94 (t, J = 8.0 Hz, 9H), 1.25 (d, J = 6.2 Hz, 3H), 1.56~2.14 (m, 6H), 2.87 (dd, J = 5.6 Hz, J = 2.2 Hz, 1H), 3.19~3.30 (m, 1H), 3.97 (t, J = 3.2 Hz, 1H), 4.01~4.04 (m, 1H), 4.18 (quint, J = 6.0 Hz, 1H), 5.76 (br s, 1H (-NH-)). FAB-MS (m/z) 456 $[M+H]^+$.

(3*S*, 4*R*)-3-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-4-[(1*R*,3*S*)-3-triethylsilyloxy-2-oxocyclohexyl]-1-(2-diphenylmethoxycarbonyl-1-hydroxyethyl)-2-azetidinone (32)

31 (660 mg, 1.46 mmol) and glyoxylic acid benzhydryl ester (343 mg, 1.46 mmol) were dissolved in toluene (13 mL) and the reaction mixture was refluxed with a condenser containing Molecular Sieves type 4A for 3 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography (toluene-EtOAc = 16:1) to give 32 as a colorless foam (0.9 g, 88%). IR ($CHCl_3$) cm^{-1} 3490, 1751, 1710; ^1H NMR ($CDCl_3$) δ 0.11 (s, 6H × 1/2 (isomer A)), 0.14 (s, 6H × 1/2 (isomer B)), 0.63~0.80 (m, 6H (mixture of isomers)), 0.89 (s, 9H × 1/2 (isomer A)), 0.95 (s, 9H × 1/2 (isomer B)), 0.96~1.38 (m, 9H (mixture of isomers)), 1.31 (d, J = 6.0 Hz, 3H × 1/2 (isomer A)), 1.37 (d, J = 6.0 Hz, 3H × 1/2 (isomer B)), 1.68~2.14 (m, 6H), 3.07~3.12 (m, 1H), 3.27~3.35 (m, 1H × 1/2 (isomer A)), 3.41~3.49 (m, 1H × 1/2 (isomer B)), 3.93~4.34 (m, 3H), 5.35 (d, J = 10.7 Hz, 1H × 1/2 (isomer A)), 5.70 (d, J = 10.7 Hz, 1H × 1/2 (isomer B)), 6.90 (s, 1H), 7.36~7.47 (m, 10H). FAB-MS (m/z) 696 $[M+H]^+$.

(3*S*, 4*R*)-3-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-4-[(1*R*,3*S*)-3-triethylsilyloxy-2-oxocyclohexyl]-1-(2-diphenylmethoxycarbonyl-1-triphenylphsphoranylideneethyl)-2-azetidinone (33)

To a solution of 32 (450 mg, 0.65 mmol) in THF (8 mL) cooled to -40 °C, 2,6-lutidine (0.23 mL, 1.95 mmol) and thionyl chloride (0.052 mL, 0.72 mmol) were added, and the reaction mixture was stirred for 30 min at the same temperature. After the usual work up of the reaction mixture, the residue was dissolved in THF (10 mL) under ice cooling. 2,6-Lutidine (0.15 mL, 1.3 mmol), NaBr (334 mg, 3.25 mmol) and triphenylphosphine (205 mg, 0.78 mmol) were successively added to the solution, and the reaction mixture was stirred

vigorously at rt for 4 h. After the usual work up, the residue was purified by silica gel chromatography (toluene-EtOAc = 8:1) to give 33 as a white solid (220 mg, 35%). IR ($CHCl_3$) cm^{-1} 1733, 1639, 1604; ^1H NMR ($CDCl_3$) δ 0.08 (s, 6H), 0.62~0.79 (m, 6H), 0.93~1.12 (m, 18H), 1.41~1.43 (m, 3H), 1.50~2.10 (m, 6H), 2.74~2.84 (m, 1H), 3.08~3.32 (m, 1H), 4.00~4.10 (m, 3H), 6.84~7.93 (m, 26H). FAB-MS (m/z) 940 $[M+H]^+$.

Benzhydryl (4*S*,8*S*,9*R*,10*S*)-4-hydroxy-10-[(1*R*)-1-hydroxyethyl]-11-oxo-1-azatricyclo-[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (34)

To a solution of 33 (220 g, 0.23 mmol) in MeCN (5 mL) under ice cooling, conc. HCl (0.04 mL, 0.46 mmol) and acetic acid (0.013 mL, 0.23 mmol) were added. After being stirred for 1 h at the same temperature, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ (1.5 mL) and partitioned between EtOAc and water, then the organic layer was washed with saturated brine twice. The residue was purified by silica gel column chromatography (toluene-EtOAc = 1:1) to give desilylated ylide as a white solid (160 mg, quant.). After this ylide was refluxed in toluene (10 mL) for 3 h, concentration of the reaction mixture and purification by silica gel chromatography (toluene-EtOAc = 1:1) gave 34 as a colorless foam (70 mg, 70% from 33). IR ($CHCl_3$) cm^{-1} 3360, 1769, 1713; ^1H NMR ($CDCl_3$) δ 1.35 (d, J = 6.2 Hz, 3H), 1.50~2.00 (m, 6H), 3.27 (dd, J = 6.6 Hz, J = 3.4 Hz, 1H), 3.32~3.46 (m, 1H), 4.19 (dd, J = 10.2 Hz, J = 3.2 Hz, 1H), 4.20~4.29 (m, 2H), 5.52 (br s, 1H (-OH)), 6.92 (s, 1H), 7.19~7.72 (m, 10H). FAB-MS (m/z) 434 $[M+H]^+$.

(4*S*,8*S*,9*R*,10*S*)-4-Hydroxy-10-[(1*R*)-1-hydroxyethyl]-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylic acid sodium salt (1c)

To a solution of 34 (70 mg, 0.16 mmol) in CH_2Cl_2 (10.5 mL) / $MeNO_2$ (3.5 mL) cooled to -20 °C, anisole (0.17 mL, 1.6 mmol) and $AlCl_3$ (1M $MeNO_2$ solution, 1.6 mL, 1.6 mmol) were added, and the reaction mixture was stirred vigorously for 1 h. After the reaction mixture was partitioned between NaOAc (407 mg, 4.96 mmol) / water (20 mL) and ether (20 mL), the aqueous layer was taken, washed with ether, and concentrated under reduced pressure to remove remaining organic solvent. Then, the residue was subjected to Diaion HP-20AG column chromatography (MeOH-water). After addition of $NaHCO_3$ (6.6 mg, 0.08 mmol) to the collected fraction, the same purification was performed again. The purified and concentrated aqueous solution was lyophilized to give 1c as a colorless foam (10 mg, 20%). IR (KBr) cm^{-1} 3380, 1740; ^1H NMR (D_2O) δ 1.28 (d, J = 6.4 Hz, 3H), 1.54~1.97 (m, 6H), 3.23~3.37 (m, 1H), 3.43 (dd, J = 6.0 Hz, J = 2.8 Hz, 1H), 4.14~4.30 (m, 3H). SI-MS (m/z) 290 $[M+H]^+$. HR-FABMS Calcd for $C_{13}H_{17}NO_5Na$ ($[M+H]^+$): 290.1004. Found: 290.1006; $[\alpha]_D$ -13.0 (c = 0.2, H_2O).

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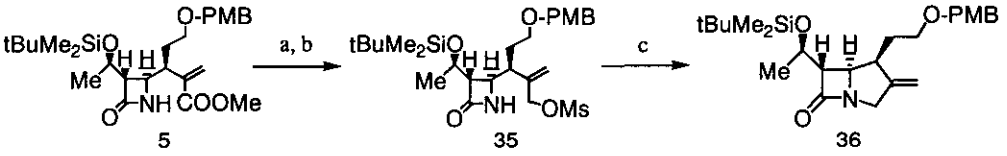
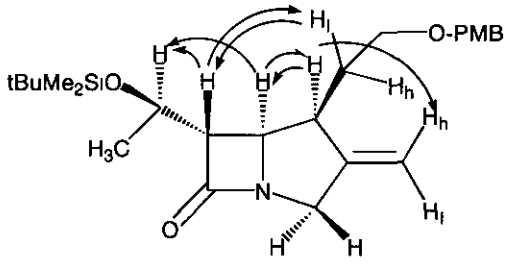


a) DIBAL-H (3 eq.), toluene, -78℃; b) MsCl, Et_3N; c) $LiN(SiMe_3)_2$, 0℃



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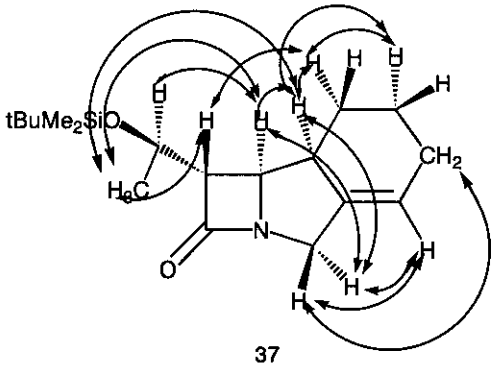

37

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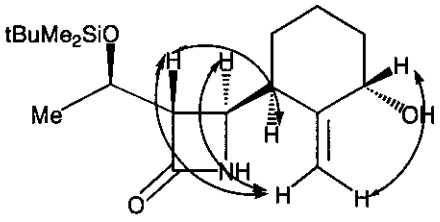
14 The stereo-configuration of the hydroxy group in **29** was determined from the following N.O.E. correlation.



29

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